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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/523,886	03/13/2000	David J. Grdina	P-01904US1	6435

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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/10/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/523,886	Grdina et al.
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 7, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-13, and 23-33* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-13, and 23-33* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' amendment filed 10-7-02 has been entered. Claims 1, 9, 10, 30 and 31 have been amended. Claims 32 and 33 have been added. Claims 14-22 have been canceled in amendment filed 2-26-02 (Paper No. 12). Claims 1, 3-13 and 23-33 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 3-13 and 23-31 remain rejected and claims 32 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting or preventing metastases by administering WR-2721 at a concentration of 50mg/kg to 150mg/kg to an animal, does not reasonably provide enablement for inhibiting or preventing metastases by administering any phosphorothioate or active metabolite thereof other than WR-2721 as disclosed, or administering WR-2721 at a concentration of 10mg/kg to less than 50mg/kg to an animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 5-1-02

(paper No. 13). Applicant's arguments filed 10-7-02 have been fully considered but they are not persuasive.

Claims 32 and 33 are newly added claims. Claims 32 and 33 specify the phosphorothioate or active metabolite thereof is WR-2721 and WR-1065, respectively.

Applicants argue that "phosphorotioate" does not refer to any compound that has phosphorus and a thio group and it refers to a discrete chemical make-up. Applicants further argue that there is no reason to doubt that the invention is not operable as disclosed in the specification and the examiner does not provide reasonable explanation as to why the scope of the claimed invention is not enabled by the disclosure (amendment, p. 10). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-1-02 (paper No. 13) and that phosphorothioic acid has the chemical formulation of H_3PO_3S and phosphorothioate is the salt of phosphorothioic acid. Additional chemical group can be added to PO_3S to form phosphorothioate. Applicants indicate phosphorothioate refers to a discrete chemical make-up but fails to clarify what discrete chemical make-up it represents. The specification fails to specifically define "phosphorothioate". The term "phosphorothioate" was given broadest reasonable interpretation in light of specification. In addition, the art teaches using c-myc antisense phosphorothioate oligonucleotide for protection against metastasis. Thus, the term "phosphorothioate" is interpreted to include any compound that has phosphors and thio-group or PO_3S as discussed above. The claims encompass any phosphorothioate compound and its active metabolite and the scope of the claims is very broad.

As discussed in the preceding Official action mailed 5-1-02 (paper No. 13), different chemical compounds could have positive or negative effects in inhibiting metastasis and the degree of tumor radioprotection afforded by WR-2721 varies with the type of tumor and assay endpoint. The specification fails to provide adequate guidance and evidence for inhibition and prevention of metastases of various tumors by using any phosphorothioate and active metabolites thereof other than WR-2721. The specification also fails to provide adequate guidance and evidence for inhibition and prevention of metastases of various tumors *in vivo* by using any phosphorothioate and active metabolites thereof, such as WR-2721, at a concentration of 10mg/kg to less than 50mg/kg. The specification must provide sufficient enabling disclosure for the claimed invention but fails to do so.

Applicants argue that Kanclerz teaches radiotherapy by using WR-2721 as radioprotector but not subcytoprotection, and Milas also teaches using WR-2721 as radioprotector. Applicants argue that both references are not relevant to the claimed invention (amendment, p. 11). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-1-02 (paper No. 13) and the following reasons:

Firstly, The term "subcytoprotection" refers to an amount that is **too low to** prevent cell killing and/or loss of function in normal tissues exposed to **radiation and chemotherapy**". Therefore, the amount of phosphorothioate, such as WR-2721, is so low that it does not prevent cell killing and some cell killing could occur in normal tissues exposed to **radiation and**

chemotherapy. However, the specification fails to specifically define at what concentration of phosphorothioate is subcytoprotective.

Secondly, Milas teaches that normal tissues usually have better protection than tumor tissues against radiation by using WR-2721 but the degree of tumor radioprotection afforded by WR-2721 varies with the type of tumor and assay endpoint. The radioprotection by radioprotector WR-2721 does not mean that all cell killing by radiation or chemotherapy are prevented and there is no cell killing after using WR-2721. The teaching of Milas reference indicates that it was unpredictable to predict radioprotection afforded by WR-2721 on various types of tumors. Further, Milas et al., 1984 (IDS-C51), as cited under 35 U.S.C. 103(a) rejection, teaches WR-2721 greatly reduces the spontaneous metastases induced by cyclophosphamide (CY) and whole body irradiation (WBI) in mice with fibrosarcoma injected i.v. into said mice. Therefore, the teachings of Milas is relevant to the claimed invention.

Thirdly, Kanclerz teaches when the radioprotector WR-2721 was given in fractioned schedules in three different doses (0.05g/kg, 0.1g/kg and 0.2g/kg for 10 consecutive days) a slight enhancement of lung metastases and suppression of extrapulmonary metastases was observed. Kanclerz measures incidence of metastases in the lungs and in other organs and shows WR-2721 decreases incidence of metastases in adrenals at highest dosage and WR-2721 at 0.4g/kg inhibits lymph node metastases. As discussed above, the radioprotection by radioprotector WR-2721 does not mean that all cell killing by radiation or chemotherapy are prevented and there is no cell killing after using WR-2721 and the specification fails to

specifically define at what concentration of phosphorothioate is subcytoprotective. Therefore, the teachings of Kanclerz is relevant to the claimed invention.

Applicants argue that the specification teaches using single and multiple doses of WR-2721 for sarcoma SA-NH and adenocarcinoma Mca-K and Oca-1 and the claims are enabled for in vivo use (amendment, p. 12, 13). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-1-02 (paper No. 13) and the reasons set forth above.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1, 3-13, 30 and 31 remain rejected and claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Milas et al., 1984 (IDS-C51) in view of Kanclerz et al., 1988 (exhibit D) and is repeated for the reasons set forth in the preceding Official action mailed 5-1-02 (paper No. 13). Applicant's arguments filed 10-7-02 have been fully considered but they are not persuasive.

Claim 32 is newly added claim and specifies the phosphorothioate or active metabolite thereof is WR-2721.

Applicants argue that Kanclerz is not enabling because Kanclerz only weight extrapulmonary tissues and does not show the treatment caused suppression of metastases. Applicants argue that Kanclerz does not show the claimed invention would work (amendment, p. 15). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-1-02 (paper No. 13).. Kanclerz teaches when the radioprotector WR-2721 was given in fractioned schedules in three different doses (0.05g/kg, 0.1g/kg and 0.2g/kg for 10 consecutive days) a slight enhancement of lung metastases and suppression of extrapulmonary metastases was observed. Kanclerz measures incidence of metastases in the lungs and in other organs and shows WR-2721 decreases incidence of metastases in adrenals at highest dosage and WR-2721 at 0.4g/kg inhibits lymph node metastases (see page, 310, 315, Table 6). Therefore, Kanclerz does show the treatment of WR-2721 caused suppression of metastases with reasonable expectation of success.

Applicants argue that only 2g/kg dose is significantly different the control and the specification also provides data measuring the number of metastases following treatment (amendment, p. 15-16). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-1-02 (paper No. 13) and the reasons set forth in the preceding paragraph. The effect of 2g/kg itself constitutes the effectiveness of WR-2721 on suppression of metastases. In fact, 0.05g/kg and 0.1g/kg doses also show significant effect in suppression of adrenal metastases (see Figure. 4). Further, the specification fails to specifically define at what concentration of phosphorothioate is subcytoprotective.

Applicants argue that both Kanclerz and Milas teach the use of WR-2721 as a radioprotector to protect normal cells from being harmed by radiation and the dosage range cited by Kanclerz teaches away from the claimed invention (amendment, p. 16-17). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-1-02 (paper No. 13) and the reasons set forth above. Kanclerz measures incidence of metastases in the lungs and in other organs and shows WR-2721 decreases incidence of metastases in adrenals at highest dosage and WR-2721 at 0.4g/kg inhibits lymph node metastases (see page, 310, 315, Table 6). Milas teaches WR-2721 abolished metastases enhancement effect of CY (metastases incidence was 9% (1/11)). Thus, Kanclerz and Milas do teaches using WR-2721 to reduce the number of metastases. Examiner does not understand why the doses range cited by Kanclerz teaches away from the claimed invention. The specification of the present application does not specifically

define at what concentration of phosphorothioate is subcytoprotective. Therefore, the doses range cited by Kanclerz does not teach away from the claimed invention.

Applicants argue that there is no reasonable expectation of success from the teachings of Kanclerz and Milas (amendment, p. 17). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-1-02 (paper No. 13) and the reasons set forth above.

5. Claims 1, 23 and 25-29 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Milas et al., 1984 (IDS-C51) in view of Kanclerz et al., 1988 (exhibit D) as applied to claims 1, 3-13, 30 and 31 above, and further in view of Golub, 1998 (US Patent No. 5,837,696) and Antras-Ferry et al., 1997 (IDS-C2) and is repeated for the reasons set forth in the preceding Official action mailed 5-1-02 (paper No. 13). Applicant's arguments filed 10-7-02 have been fully considered but they are not persuasive.

Applicants argue that there is no motivation to combine Milas and Kanclerz with Golub and Antras-Ferry because Kanclerz and Milas teaches radiotherapy and Golub and Antras-Ferry do not suggest or teach administering a phiosphorothioate at a subcytoprotective dose for reducing the number of metastases in an animal (amendment, p. 18-19). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-1-02 (paper No. 13) and the reasons set forth above under 35 U.S.C. 103(a) rejection of claims 1, 3-13 and 30-32. Kanclerz and Milas do teaches using WR-2721 to reduce the number of metastases in an

animal. The specification of the present application does not specifically define at what concentration of phosphorothioate is subcytoprotective. Golub teaches that MMP expression, especially gelatinase expression, is associated with cancer invasiveness or metastasis, and CMT-3 inhibits the expression of MMP-2 and MMP-9 in cancer cells *in vitro*. Antras-Ferry teaches that OPZ is a potent chemoprotective agent against chemical induced carcinogenesis in several animal model and OPZ induces the transcription of the manganese superoxide dismutase (MnSOD) in a dose-dependent manner. Thus, one having ordinary skill at the time of the invention would have been motivated to practice the claimed invention in order to monitor the effectiveness of the phosphorothioate and active metabolite thereof in reducing the number of metastasis in tumor bearing animals by measuring the activity of MMP-2 and MMP-9, and gene expression of MnSOD as taught by Golub and Antras-Ferry with reasonable expectation of success.

6. Claims 1, 23 and 24 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Milas et al., 1984 (IDS-C51) in view of Kanclerz et al., 1988 (exhibit D) as applied to claims 1, 3-13, 30 and 31 above, and further in view of Gately et al., 1997 (IDS-C13) and is repeated for the reasons set forth in the preceding Official action mailed 5-1-02 (paper No. 13). Applicant's arguments filed 10-7-02 have been fully considered but they are not persuasive.

Applicants argue that there is no motivation to combine Milas and Kanclerz with Gately and Gately does not teach administering a phiosphorothioate at a subcytoprotective dose for

reducing the number of metastases (amendment, p. 20). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-1-02 (paper No. 13) and the reasons set forth above under 35 U.S.C. 103(a) rejection of claims 1, 3-13 and 30-32. Kanclerz and Milas do teaches using WR-2721 to reduce the number of metastases in an animal. The specification of the present application does not specifically define at what concentration of phosphorothioate is subcytoprotective. Gately teaches angiostatin inhibits angiogenesis *in vitro* and *in vivo* and suppresses the growth of Lewis lung carcinoma metastases. Thus, one of ordinary skill at the time of the invention would have been motivated to practice the claimed invention in order to monitor the effectiveness of the phosphorothioate and active metabolite thereof in reducing the number of metastasis in tumor bearing animals by measuring stimulation of angiostatin with reasonable expectation of success.

Conclusion

No claim is allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.